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Incremental Value of Secretin-Enhanced Magnetic Resonance Cholangiopancreatography in Detecting Ductal Communication in a Population with High Prevalence of Small Pancreatic Cysts

Neda Rastegar, MD¹, Luciana G. Matteoni-Athayde, MD¹, John Eng, MD¹, Naoki Takahashi, MD², Eric P. Tamm, MD³, Koenraad J. Mortele, MD⁴, Sapna Syngal, MD⁵, Daniel Margolis, MD⁶, Anne Marie Lennon, MB PhD¹, Christopher L. Wolfgang, MD PhD¹, Elliot K. Fishman, MD¹, Ralph H. Hruban, MD¹, Michael Goggins, MD¹, Marcia I. Canto, MD MHS¹, and Ihab R. Kamel, MD PhD¹

¹Departments of Medicine (Gastroenterology) and Radiology, The Sol Goldman Pancreatic Cancer Research Center, Johns Hopkins Medical Institutions

²Mayo Clinic

³MD Anderson Cancer Center

⁴Beth Israel Deaconess Medical Center

⁵Dana Farber Cancer Institute

⁶University of California Los Angeles

Abstract

Purpose—We investigated the incremental diagnostic yield of S-MRCP in a population with high prevalence of small pancreatic cysts.

Methods—Standard MRCP protocol was performed with and without secretin using 1.5 T unites in subjects undergoing pancreatic screening because of a strong family history of pancreatic cancer as part of the multicenter Cancer of the Pancreas Screening-3 trial (CAPS 3). All studies were reviewed prospectively by two independent readers who recorded the presence and number of pancreatic cysts, the presence of visualized ductal communication before and after secretin, and the degree of confidence in the diagnoses.

Result—Of 202 individuals enrolled (mean age 56 years, 46% males), 93 (46%) had pancreatic cysts detected by MRCP, and 64 of the 93 had pre-and post-secretin MRCP images available for comparison. Data from the 128 readings show that 6 (6/128 = 4.7%) had ductal communication visualized only on the secretin studies compared to pre-secretin studies (odds ratio 1.28, p = 0.04).

Address for Correspondence: Ihab R Kamel, MD, PhD, Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins Hospital, 1800 Orleans Street, MRI 143, Baltimore, MD 21287, (410) 955-4567, (410) 955-9799 (fax), ikamel@jhmi.edu.

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In addition, there was a statistically significant increase in confidence in reporting ductal communication after secret n compared to before secret (p < 0.0005).

Conclusion—At 1.5 T MRI, the use of secretin can improve the visualization of ductal communication of cystic pancreatic lesions.

Keywords

Cyst; Magnetic resonance imaging; Neoplasm; Pancreas; Screening; Secretin

Introduction

The majority of pancreatic cancer cases are sporadic, however up to 10% are considered to be inherited (1,2). Pancreatic cancer is the fourth leading cause of cancer death in USA (1,3), and its incidence has increased over the last 8 years. It is associated with a high mortality rate and about 38,460 deaths are estimated in 2013 (4). Individuals with multiple first-degree relatives with pancreatic cancer as well as subjects with hereditary pancreatitis, carriers of germline mutations in *BRCA2, ATM, p16, PALB2* and mismatch repair genes and those with Peutz–Jeghers syndrome (PJS) have a higher risk of developing pancreatic cancer than the general population (5). Pancreatic screening studies of high risk individuals identified a high prevalence of pancreatic lesions, particularly pancreatic cysts in these individuals (6–12). Pancreatic screening of high risk individuals was also recommended at a recent consensus conference, even though the method and frequency of screening were not defined (1).

Pancreatic intraepithelial neoplasia (PanIN) is by far the most common precursor lesion of pancreatic ductal adenocarcinoma, followed by two cystic precursor lesions, intraductal papillary mucinous neoplasm (IPMN) and mucinous cystic neoplasm (MCN) (6,13). PanIN can only be diagnosed microscopically in the resected pancreas. IPMNs and MCNs can be identified radiologically. Given that MCN lesions are rare, the main diagnostic challenge is to accurately distinguish IPMN from benign cystic neoplasms of the pancreas such as serous cystadenomas. In this scenario, visualizing the communication of the lesion with the pancreatic duct is a key diagnostic feature, since it is essentially only observed in cases of side branch IPMNs (SB-IPMN) (14).

The majority of pancreatic cystic lesions can be detected with magnetic resonance (MR) imaging with high spatial resolution and soft-tissue contrast. Furthermore, magnetic resonance cholangiopancreatography (MRCP) is a non-invasive and an accurate modality in detecting, localizing and classifying IPMNs (14–16).

Some centers have recommended the use of intravenous secretin stimulation as part of their MR protocol to evaluate pancreatic cystic lesions (14–16). Secretin is a 27-amino acid polypeptide hormone secreted by the duodenal mucosa in response to luminal acid (17). One of its numerous physiological effects is to stimulate pancreatic duct epithelial cells to produce bicarbonate-rich fluid. Due to this mechanism of action, secretin is frequently used as part of the MR protocol to improve visualization of the pancreatic duct. Secretin increases the caliber of the pancreatic duct, permitting better assessment of ductal strictures,

irregularities and anatomic variants. It has also been recently demonstrated to be of value in patients with pancreatitis (3) Secretin-enhanced MRCP may also delineate to a better degree the communication of a cystic lesion with the ductal system, allowing accurate diagnosis of IPMNs (15,16). The purpose of our study was, therefore, to evaluate the incremental value of secretin-enhanced MRCP (S-MRCP) in detecting ductal communication in a population with high prevalence of small pancreatic cysts.

Material and Methods

This was a prospective multicenter study performed at five tertiary academic medical centers (_______). The study was undertaken in compliance with the HIPAA and Institutional Review Board approval was obtained from all participating sites. All subjects provided an informed consent.

Patient Population

Data collected in this study were part of the American Cancer of the Pancreas Screening (CAPS) 3 study (1). Three groups of asymptomatic high-risk individuals were included in the study. They were identified by each site either through their participation in pancreatic cancer family registries such as the National Familial Pancreas Tumor Registry (NFPTR), or from referrals generated by notices of the study through various websites (1,18–21). Risk categories included PJS patients, germline BRCA2 mutation carriers with at least 1 affected first- or second-degree relative with pancreatic cancer, and first degree relatives of patients with familial pancreatic cancer. None of these patients had diseases that could affect pancreatic exocrine function including chronic liver diseases, renal diseases, pancreato-biliary diseases, or diabetes mellitus.

MRI Acquisition technique and contrast

A standardized protocol for MRI was performed at 1.5 Tesla unites (Siemens Avanto and GE Signa HDx) using a phased-array torso coil. The protocol included axial T2 weighted fat saturated images (4-6 mm, TR 4000-6000, TE 90-100), at least 6 thick slab (40-50 mm, TR 4500, TE 500–700) heavily T2 weighted magnetic resonance cholangiopancreatography (MRCP) images obtained in the straight coronal plane, one before and every minute for five minutes after intravenous administration of human synthetic secretin (0.2 ug/kg; ChiRhoClin, Inc, Burtonsville, MD). The sequence was repeated in the coronal oblique planes. Thin section (1-3 mm, TE 150-200, overlap 0-50%) respiratory triggered or navigator coronal 3D FS TSE images are also obtained before and 5 minutes after secretin administration. Breath-hold unenhanced and contrast-enhanced (0.1 mmol/kg intravenous gadopentetate; Magnevist; Bayer, Wayne, NJ) T1-weighted (T1W) three-dimensional fat suppressed spoiled gradient-echo images (field of view, 320-400 mm; matrix, 192×160 ; slice thickness, 2.5 mm; repetition time, 5.77 ms; echo time, 2.77 ms; received bandwidth, 64 kHz; flip angle, 10°) in the arterial (20 s), portal venous (70 s), and delayed phase (3 min) were also obtained. Two subjects reported adverse events related to the use of secretin in this study. One patient had a mild reaction in the form of itching, and the other patient had nausea.

Image Analysis

The MRI studies were de-identified and prospectively reviewed at (______). Initial review was by a single MR radiologist (____) with 14 years of experience in abdominal imaging who was blinded to clinical findings. The presence and number of pancreatic cysts was recorded as well as the size of the largest cyst. Subsequently, all MRI studies with cystic lesions of the pancreas that included thin section MRCP pre and post-secretin were reviewed by 2 radiologists specialized in abdominal imaging, with 3 years (____) and 14 years (___) of experience. Both radiologists, who were blinded to the diagnosis, reviewed the largest (dominant) pancreatic cystic lesion and independently recorded the presence of communication of the lesion with the main pancreatic duct (MPD) and confidence in the presence or absence of ductal communication. These 2 features were analyzed first on the pre-secretin images alone. Post secretin images were analyzed separately after 2 weeks to reduce recall bias. The degree of confidence in the presence or absence of ductal communication was scored on a 5 –point scale: 1 (20%), 2 (>20% – 40%), 3 (>40% – 60%), 4 (>60% – 80%) and 5 (>80%).

Statistical Analysis

Continuous sociodemographic variables are presented as mean \pm standard deviation (SD) and categorical variables as proportions or percentages. Continuous and categorical sociodemographic variables were compared using the Student t- test and chi- squared tests, respectively.

The relationship between visualization of ductal communication and the presence of secretin was examined with a logistic regression model. The model was adjusted for potential interreader differences, statistical interaction between reader and secretin administration, and statistical correlation arising from having both readers interpret the same case set. The relationship between interpretation confidence and secretin administration was examined with an ordered logistic regression model having the same covariates as the preceding logistic regression model. All statistical analyses were performed using the Stata statistical software package (version 10, Stata Corp., College Station, Texas). A p-value of <0.05 indicated statistical significance.

Results

Demographic Information

Of 202 asymptomatic HRIs enrolled and imaged, 93 (46%) were found to have at least one pancreatic cyst. Demographic information of the entire cohort and the subjects with and without pancreatic cysts is shown in Tables 1 and 2. Average cyst size was $7 \pm SD 4 \text{ mm} (2-20 \text{ mm})$. The presence of cystic lesions of the pancreas increased with age (p<0.001) in our population. No association was found between the presence of pancreatic cysts and gender, ethnicity or risk group (Table 2). Forty-nine (52.7%) of the 93 subjects with a cyst had one or two cystic lesions, while 6 (6.5%) subjects had 12 or more lesions.

Of the 93 patients with cystic lesion of the pancreas identified by S-MRCP, 64 were included in the analysis that assessed the incremental value of S- MRCP in the screening of

asymptomatic individuals with high risk of pancreatic cancer. 29 patients were excluded from this analysis either because their MR study quality was classified as poor (3 patients) or because thin section MRCP either pre or post-secretin were not acquired (26 patients).

Value of Secretin in Visualizing Ductal Communication

On the 64 pre-secretin images Reader 1 (with 3 year experience) visualized communication between the largest cyst and the MPD in 31 cases (48.4%), while no communication was observed in the remaining 33 lesions (51.6%). Reader 2 (with 14 years experience) detected communication between the largest cyst and the MPD in 33 of the 64 cases (51.6%) on the pre-secretin images, while no communication was visualized in the remaining 31 lesions. Analysis of images after the administration of secretin allowed Reader 1 and Reader 2 to visualize ductal communication which was not identified on pre-secretin images in an additional 4 (6.3%) and 2 (3.1%) exams, respectively (Table 2, Figure 1). Data from both readers demonstrated ductal communication between the largest cyst and the MPD in 6 additional cases out of their 128 interpretations (4.7%). Post-secretin imaging was associated with a greater likelihood of visualizing ductal communication compared to pre-secretin imaging (odds ratio 1.28, p = 0.04). Overall, there was no statistically significant difference between readers for visualizing ductal communication (p = 0.2). No case had better demonstration of ductal communication on the pre-secretin dataset compared to the post-secretin images.

Value of Secretin in Improving Confidence in Diagnosis

The effect of secretin on the degree of confidence on the diagnosis of visualizing ductal communication between the lesion and MPD was tested. Reader 1 scored ductal communication on pre-secretin images with a confidence level of 3, 4 and 5 in 5 (7.8%), 22 (34.4%) and 37 lesions (57.8%), respectively. Reader 2 scored ductal communication on pre-secretin images scored a confidence level of 3, 4 and 5 in 8 (12.5%), 14 (21.9%) and 41 lesions (64.1%), respectively. No case was scored a confidence level of 1 or 2.

After secretin, 50 (78.1%) and 49 (76.6%) cases were diagnosed with the greater level of confidence by Reader 1 and 2, respectively. Neither of the readers scored the post-secretin images with a level 1 or 2 confidence. In the ordered logistic regression model, interpretation of post-secretin images was associated with a much greater level of confidence than presecretin imaging (p < 0.0005). There was no statistically significant difference in confidence ratings between the two readers.

Discussion

Pancreatic cysts have become an increasingly common diagnosis over the last decade in part thanks to increase in the use of high resolution abdominal imaging. Individuals with multiple first-degree relatives with pancreatic cancer have a very high incidence of pancreatic cysts (13,22). The goal of screening is to detect high grade benign precursor lesions such as high risk IPMNs, that can be operatively treated. The radiological assessment of pancreatic cysts can be challenging, particularly the differentiation of IPMNs from those pancreatic cysts with little malignant potential such as serous cystadenomas. Visualizing ductal

communication of a pancreatic cyst is very helpful since it supports the diagnosis of IPMN. The objective of this study was to quantify the incremental value of S-MRCP in detecting ductal communication in a population with high prevalence of small pancreatic cysts. Only high risk subjects were included in this study.

This study has several interesting findings. First, the presence of pancreatic cystic lesions increased with patient age. This is similar to what was reported in a prior study by Lee et al, where the incidence of pancreatic cysts increased form 7.9% below the age of 70 to 40.2% above 70 years of age (23). Second, we found no association between the presence of pancreatic cysts and gender, ethnicity or type of high risk group (p-value = 0.67). Third, we found that secretin improved visualization of ductal communication and also increased the reader's confidence in making a diagnosis of IPMN.

Secretin stimulates pancreatic exocrine secretions causing a temporary dilatation of the pancreatic ducts. This allows for better visualization of the ducts at MRCP. Few prior reports have demonstrated the added value of secretin in diagnosing pancreatic ductal anatomy and pancreatic pathology (16). A recent phase 3 multicenter studies demonstrated that the use of secretin in patients with pancreatitis resulted in significantly improved sensitivity in detecting ductal abnormalities, with minimal loss of specificity (3). However, the diagnostic utility of secretin in the diagnosis of pancreatic cysts remains debated in part because there have not been controlled studies that have assessed the added diagnostic value of secretin. Our study demonstrated that the administration of secretin improved visualization of ductal communication of a cystic lesion in 4.6% of patients (p=0.04) with pancreatic cysts. In addition, both readers regardless of their experience had higher confidence in making the diagnosis of IPMN using secretin compared to their confidence without using secretin. A recent study by Purysko et al. evaluated the value of secretin in SB-IPMN patients and non-IPMN subjects (control) (24). They reported that Secretin administration did not improve the demonstration of communication between the SBIPMN and the MPD. The difference between their study and our study is that the time of acquisition of the post-secretin HASTE images was beyond the time of maximal effect of secretin on the pancreatic ductal system (10 minutes in their study compared to 5 minutes in the current study) and most of the secreted fluid has already passed in the duodenum. This potentially affects the visualization of duct communication on the post-secretin HASTE images and explains the lack of significant difference in duct communication and the lesion size on the pre- and post-secretin HASTE images.

In spite of the added value of using secretin there are several disadvantages to using it routinely in MRI. The added cost, the potential for side effects of secretin and the extended scanning time should be considered when considering S-MRCP. These potential disadvantages should be balanced with the usefulness of detecting a curable precursor lesion. The majority of small pancreatic cysts remanin stable and do not develop cancer (9,25–27). However, when an adenocarcinoma arises in association with an IPMN, the IPMN and the invasive carcinoma almost always harbor the same genetic alterations, supporting the hypothesis that IPMNs are a precursor to invasive adenocarcinomas (28–30). Detection of early precursor lesions could lead to decreased morbidity and mortality from pancreatic adenocarcinoma. Therefore, regardless of the cost and time, it may be useful to

use secretin in high-risk patients to detect early-stage pancreatic cancer or high-grade benign noninvasive precursor neoplastic lesions such as IPMNs (31). In addition, it may be advantageous to use secretin in patients based on their symptoms, risk factors and previous imaging findings. Clinicians should also be aware that, especially in females, small non communicating pancreatic cysts can be mucinous cystic neoplasm, which are considered premalignant lesions. Thus, in high risk patients small non-communicating cysts may still be followed-up (32).

There are several limitations to this study. First, the gold standard for diagnosing an IPMN is surgical pathology but most patients with small IPMNs such as those in this study do not undergo surgical resection of their cyst(s). These patients do not undergo ERCP routinely either, unless there is a need for diagnostic or therapeutic intervention. This is due to the high risk of pancreatitis associated with ERCP (1). However, we considered the non S-MRCP sequences as the standard of reference in this study, and we compared visualization of ductal communication to S-MRCP. In addition, routine utilization of S-MRCP in high risk patients has been recommended by Salvia, et al (33), who reported high reliability of S-MRCP in correctly diagnosing branch duct IPMN. Endoscopic ultrasound, without or cyst aspiration analysis can help determine the nature of the pancreatic cyst but this is not performed in the current study due to the small size of cysts (mean 7 mm). Also, endoscopic ultrasound is more invasive than SMRCP, is operator dependent, and maybe associated with false positive results (33). Our study was performed using 1.5T units for this multi-institutional study to standardize the MRCP protocol using the most widely available magnet. Future studies should be performed to assess the validity of our results at 3T units.

Conclusion

With 1.5 T MRI, the use of secretin improved visualization of ductal communication of a cystic lesion in 4.7% of patients with cysts. This incremental increase in visualizing ductal communication was also associated with increasing the reader's confidence in making a diagnosis of IPMN.

The incremental value of secretin in screening subjects for IPMN could potentially offset the added cost and time for additional sequences. Radiologists should decide on the cost/benefit ratio of using secretin in such cases.

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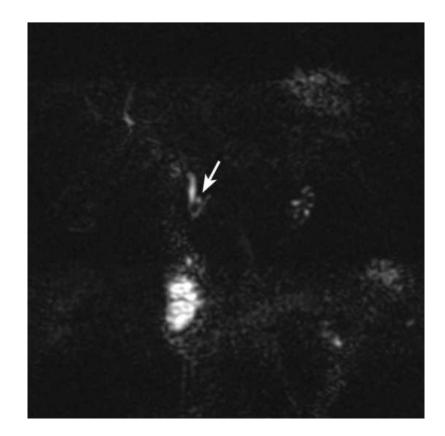
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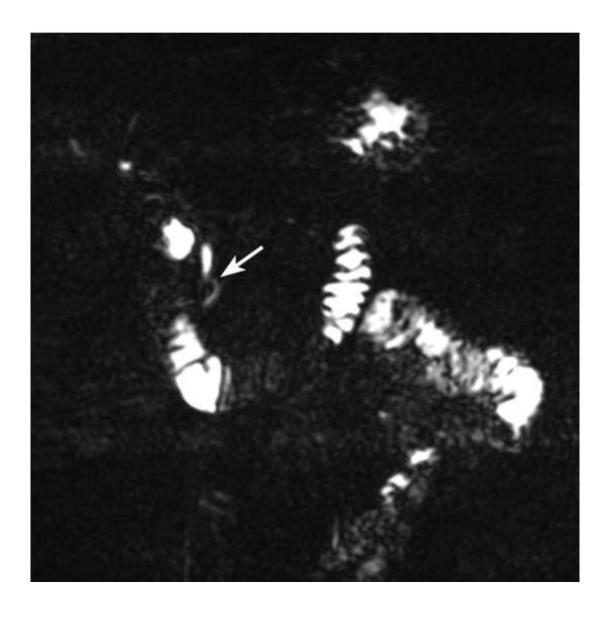
Highlights				
1.	Secretin improved visualization of ductal communication of a cystic pancreatic lesion.			
2.	No association between cysts and gender, ethnicity or type of high risk.			
3.	Incremental value of secretin could offset the added cost and time.			

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Figure 1.

Thin section (1-mm) MRCP before (A) and 5 min after secretin (B, C). Notice a 5 mm cyst in the region of the head of the pancreas (arrow in A). Neither of the readers visualized communication of the cyst with the pancreatic duct before secretin. After secretin both readers had high confidence (score of 5) in visualizing ductal communication (arrow in B). Notice increasing pancreatic secretions in duodenum and small bowel post secretin.

Table 1

Demographics information of the entire cohort

Age (yrs)	
Mean ± SD	56 +/- 10
Range	27–79
Gender (%)	
Male	93 (46.0)
Female	109 (54.0)
Ethinicity (%)	
Caucasian	198 (98.0)
Black/African American	2 (1.0)
Hispanic	1 (0.5)
Indian	1 (0.5)
Medical Center (%)	
	121 (59.9)
	46 (22.8)
	20 (9.9)
	15 (7.4)
Risk Categories (%)	
FPC relative (3 affected, 1 FDR, 2 SDR minimum)	108 (53.5)
FPC relative (2 affected FDR)	70 (34.7)
Germline mutation carrier BRCA2 (with close relative with PC)	20 (9.9)
Germline mutation carrier p16 (FAMMM)	3 (1.5)
Peutz-Jegher syndrome	1 (0.5)

Table 2

Difference in demographic information for patients with and without pancreatic cysts

	Presence of Pancreatic Cystic Lesion		
	No	Yes	p value
Age (yrs)			
Mean ± SD	53 ± 9	60 ± 9	< 0.001
Gender			
Male	52	41	0.607
Female	57	52	
Ethnicity			
Caucasian	107	91	
Black/African American	1	1	0.564
Hispanic	1	0	0.364
Indian	0	1	1
Risk Categories			
FPC relative (3 affected, 1 FDR, 2 SDR minimum)	61	47	
FPC relative (2 affected FDR)	37	33	
Germline mutation carrier BRCA2 (with close relative with PC)	9	11	0.676
Germline mutation carrier p16 (FAMMM)	2	1	
Peutz-Jegher syndrome	0	1	